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Patient experiences of digital ulcer development and evolution in systemic sclerosis

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Conflicts of interest

Michael Hughes - has received speaker honoraria (<$10,000) from Actelion Pharmaceuticals. John Pauling - has received speaker's honoraria and research grant support (>$10,000) from Actelion pharmaceuticals. Dr Pauling has undertaken consultancy work for Actelion pharmaceuticals and Boehringer Ingelheim. Jennifer Jones - none. Christopher Denton - has received research grants from GlaxoSmithKline, CSL Behring, and Inventiva and consulting fees from Roche, Actelion, GlaxoSmithKline, Sanofi, Inventiva, CSL Behring, Boehringer Ingelheim, Leadiant, Galapagos and Bayer (all <$10,000). Robyn Domsic - consulting for Eicos Sciences (<$10,000). Tracy Frech - none. Ariane Herrick - has undertaken consultancy work for Boehringer-Ingelheim, Camurus and Gesynta, has received research funding from Gesynta, and speaker's fees from Actelion (Gesynta research >$10,000). Dinesh Khanna - is a consultant to Actelion, Acceleron, Arena, Bayer, Boehringer Ingelheim, Bristol-Myer Squibb, CSL Behring, Chemomab, Corbus, GSK, Genentech/ Roche, Galapagos, Merck, Mitsubishi Tanabi; he has received grants as part of investigator-initiated trials (to the University of Michigan) from Bayer, Bristol- Myer Squibb, and Pfizer; and has stock options in Eicos Sciences, Inc (all (all <$10,000 apart from CSL, Corbus, and Boehringer Ingelhem >$10,000). Marco Matucci-Cerinic - speaking honoraria for Actelion and Biogen (<$10,000). Lorraine McKenzie - none. Lesley Ann Sakettkoo - research support and consultation relationships with Boehringer Ingelheim (<$10,000), CSL Behring (>$10,000), Eicos Sciences (<$10,000), Mallinckrodt (>$10,000), United Therapeutics (>$10,000). Rachael Gooberman-Hill - none. Andrew Moore - none.

Rheumatology key message

- SSc patients can predict new digital ulcers and symptoms change during ulcer evolution and healing.

SIR, painful digital ulcers (DUs) are common in patients with systemic sclerosis (SSc) and often refractory to treatment (1,2). DUs are generally considered to be the result of tissue ischaemia, in particular, those which occur on the fingertips (2). Other drivers of pathogenesis have been proposed for extensor DUs and for ulcers related to calcinosis cutis, although all SSc-DUs are considered to share an important (and potentially treatable) ischaemic aetiology (3–5). Little is known about the earliest 'pre-clinical' stage of DU evolution prior to the development of overt tissue damage or about how symptoms evolve during DU development and healing. The patient experience of SSc-DUs is highly complex and multi-faceted (6). We have recently reported a multicentre qualitative study that identified 5 major inter-related themes (and sub-themes) which characterise the patient experience of SSc-DUs: 'Disabling pain and hypersensitivity', 'Deep and broad-ranging emotional impact', 'Impairment of physical and social activity', 'Factors aggravating occurrence, duration and impact' and 'Mitigating, managing and adapting' (7). The aim of the present analysis was to understand patients' perceptions and beliefs about DU pathogenesis (in order to provide novel insights for clinical practice and future clinical trial design), and to identify relevant domains for core outcome sets for SSc-DU assessment.

Our methodological approach has been described previously [AC&R]. In brief, 29 patients with a confirmed diagnosis of SSc participated in 4 focus groups across the United Kingdom (Bath, Manchester and London) [7]. The study was approved by the East Midlands – Nottingham 1 research Ethics Committee (REC reference – 18/EM/0018) and all participants provided written, informed consent. Patients had a broad spectrum of prior DU experiences: 1 previous DU (n=3), 2-4 previous DUs (n=9) and ≥5 previous DUs (n=17). The mean (SD) age of patients was 59.9 (13.3) years, two thirds of patients were female (n=20), and the majority had limited cutaneous SSc (n=20). The mean (SD) disease duration (defined as time from first non-Raynaud's phenomenon symptom) duration was 12.8 (9.7) years. The majority (n=27) of patients had 'late' disease which was defined as ≤3 years since their first non-Raynaud's phenomenon symptom. The majority were receiving treatment with vasodilator medication for SSc-vasculopathy (including DU disease): calcium channel blockers (n=10), phosphodiesterase type-5 inhibitors (n=18) and endothelin receptor antagonists (n=9).

Focus groups were conducted using a bespoke topic guide and patients were recruited using a purposive sampling framework. Focus groups were audio recorded and anonymised transcripts were analysed using inductive thematic analysis (7). The present analysis reports patient perceptions and beliefs about DU pathogenesis and natural history.

Three major themes emerged which encompassed patients' perceptions and beliefs on DU pathogenesis.

Theme 1 – Underlying causes of SSc-DUs: Most participants believed that there was a reason for an ulcer to develop rather than their occurrence being haphazard. Reasons included both 'external' and 'internal' precipitating factors. 'External' causes included trauma, exposure to water, chemicals or infection, cold or change in temperature, and from cuts or skin splitting (Q1-3). 'Internal' causes were 'poor circulation' including from Raynaud's phenomenon, calcinosis, and the residual effects (e.g. residual ischaemia) of previous ulcers rendering certain areas of the fingers susceptible to further ulceration (Q4-6).

Theme 2 – Symptoms prior to SSc-DU emergence: The majority of participants reported that they could recognise when an ulcer was about to emerge. The most common symptom was pain below the skin, often described as an internal pressure (Q7-8). Some participants also reported physical skin signs (e.g. a white patch with preserved overlying epithelialisation) which would subsequently break down/ulcerate (Q9-10).

Theme 3 – Patient experiences during DU evolution and healing: This was variable between participants. Surface characteristics ranged from being moist (including overt pus) to dry with a superficial crust, and occasionally with a central 'core' (Q11-14). Associated pain during ulcer healing also varied significantly between the participants.

Our data provide novel patient-perceived insights into the pathogenesis and natural history of SSc-DU. The emergence of SSc-DUs is not considered a random event and many patients have explanations for, and sometimes can anticipate development of new ulcers. These observations could be used to develop behavioural approaches to help prevent DU such as avoidance of severe cold, hand hygiene and avoidance of mechanical injury. The sites of previous DU may represent ischaemic foci, vulnerable to further ulceration and may guide local therapies such as botulinum toxin or topical nitrates as secondary prevention. To our knowledge, we are the first to describe a 'pre-ulcer' stage which could provide a 'window of opportunity' to intervene before the onset of overt tissue damage and ulceration. Relevant to clinical trial design, DU symptoms differ significantly at the time of SSc-DU emergence, and during DU evolution and healing, which has important implications for the development of patient-reported outcome instruments for assessing SSc-DUs.

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Table 1: Quotes supporting the themes which encompassed patients' development and evolution. Quotes (Q) are sequentially cited in the text and are identified by subject (participant) number and location: Bath (B), Manchester (M) and London (L) 1&2 focus groups.

Theme		*Q*	*Subject*	*Quotation*
Underlying causes of DUs	Trauma	1	P3 M1:	I just find it with a knock … I've had a lot of minor ones but only really one big one, but it's always through trauma like touching something or, you know, if you just get your car keys and you catch it on a key or something
	Chemicals	2	P4 B1:	I also won't touch work surfaces at work because they use chemicals on them, and it's sticky, and that can really start my fingers off. So I don't use anything…Very careful about anything in the house, but I found when I go to work, if I put my finger down and think oh, they've polished it, they never clean it, they just polish it and those sorts of things can irritate the skin and start… Yeah, you know you go somewhere and you don't know if a chemical's been used to soak or clean the surfaces, actually it's something that starts them off
	Cuts or skin splitting	3	P1 M1:	it doesn't appear for no reason, there's usually a cut or a little where I've caught it somewhere, it usually turns into an ulcer. Yeah, it's never just appeared for no reason, it's always been a cut, you know
	Poor circulation	4	P8 L2:	For me it's lack of blood, lack of blood
	Calcinosis	5	P2 M1:	The calcium seems to come white, the calcium and then it gets infected and it turns into an ulcer
	Effect of previous ulcers	6	P4 B1:	the ulcers are only breaking open where I've had previous damage, obviously the fingers are compromised
Symptoms prior to DU emergence	Pain and pressure	7	P5 M2:	it just looks like a, it starts off with a very, very uncomfortable kind of hypersensitivity where again you think, oh it's going to come and you see like a little black dot and you think I've no idea what this is, but then it, it builds into what looks like an abscess maybe under your nail
		8	P6 B1:	I've definitely had sort of a feeling and with nothing there, that something's going to happen. And then it'll get really sore and it, with me, it just sort of broke into a yellow gungy mess
	Physical changes	9	P5 L1:	Yeah, for me I get that kind of, like, it kind of looks, looks like a whitish, but it's not a full on ulcer yet. … I think they have their own life, once you've got one coming it's going to come and live out its life before it goes
		10	P7 L2:	it's almost like a weird infection, it starts off dry and I think it works its way in, in to the finger more and more, it feels like it's touching the nerve and it's like the…whole thing opens up
Patient experiences during DU evolution and healing	Ulcer characteristics	11	P4 B1:	It goes into like a white spot and then that will break down and then that will weep
		12	P7 B1:	Normally the skin of whichever finger's affected will harden. And that will almost turn into like a big kind of scab, or core if you like, and if that core is knocked out or removed in anyway shape, or form then it's properly painful and if you just touch it on anything it's agonising
		13	P5 L1:	I find, you know when that scab comes off underneath it is quite, it can be quite moist, like almost pus looking
		14	P1 L1	They kind of scab eventually don't they? They start off moist and then become a scab and dry up."